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(54) Title: CRYSTALLINE FORMS OF PITAVASTATIN CALCIUM

(57) Abstract: The present invention is directed to new crystalline forms of Pitavastatin hemicalcium salt, referred to hereinafter as polymorphic Forms A, B, C, D, E and F, as well as the amorphous form. Furthermore, the present invention is directed to processes for the preparation of these crystalline forms and the amorphous form and pharmaceutical compositions comprising these crystalline forms or the amorphous form.

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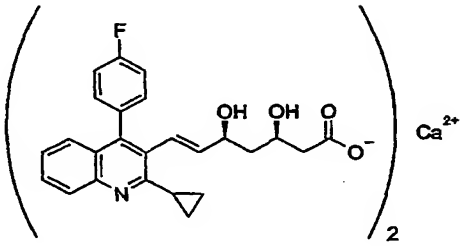
CRYSTALLINE FORMS OF PITAVASTATIN CALCIUM

The present invention is directed to new crystalline forms and the amorphous form of Pitavastatin calcium, processes for the preparation thereof and pharmaceutical compositions comprising these forms.

The present invention relates to new crystalline forms and the amorphous form of Pitavastatin calcium. Pitavastatin is also known by the names NK-104, Itavastatin and Nisvastatin. Pitavastatin calcium is known by the chemical name: (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt. Pitavastatin calcium has the following formula:



Pitavastatin calcium has recently been developed as a new chemically synthesized and powerful statin by Kowa Company Ltd, Japan. On the basis of reported data, the potency of Pitavastatin is dose-dependent and appears to be equivalent to that of Atorvastatin. This new statin is safe and well tolerated in the treatment of patients with hypercholesterolaemia. Significant interactions with a number of other commonly used drugs can be considered to be extremely low.

Processes for the preparation of Pitavastatin are described in EP-A-0304063 and EP-A-1099694 and in the publications by N. Miyachi et al. in Tetrahedron Letters (1993) vol. 34, pages 8267-8270 and by K. Takahashi et al. in Bull. Chem. Soc. Jpn. (1995) vol. 68, 2649-2656. These publications describe the synthesis of Pitavastatin in great detail but do not describe the hemicalcium salt of Pitavastatin. The publications by L.A. Sorbera et al. in

Drugs of the Future (1998) vol. 23, pages 847-859 and by M. Suzuki et al. in Bioorganic & Medicinal Chemistry Letters (1999) vol. 9, pages 2977-2982 describe Pitavastatin calcium, however, a precise procedure for its preparation is not given. A full synthetic procedure for the preparation of Pitavastatin calcium is described in EP-A-0520406. In the process described in this patent Pitavastatin calcium is obtained by precipitation from an aqueous solution as a white crystalline material with a melting point of 190-192°C. It is known that pharmaceutical substances can exhibit polymorphism. Polymorphism is commonly defined as the ability of any substance to have two or more different crystal structures. Drug substances may also encapsulate solvent molecules when crystallized. These solvates or hydrates are referred to as pseudopolymorphs. It is also possible that the amorphous form is encountered. Different polymorphs, pseudopolymorphs or the amorphous form differ in their physical properties such as melting point, solubility etc. These can appreciably influence pharmaceutical properties such as dissolution rate and bioavailability. It is also economically desirable that the product is stable for extended periods of time without the need for specialized storage conditions. It is therefore important to evaluate polymorphism of drug substances. Furthermore, the discovery of new crystalline polymorphic forms of a drug enlarge the repertoire of materials that a formulation scientist has with which to design a pharmaceutical dosage form of a drug with a targeted release profile or other desired characteristics. We now have surprisingly found novel crystalline forms of Pitavastatin calcium, herein designated as form A, B, C, D, E and F, and the amorphous form of Pitavastatin calcium.

Accordingly, the present invention is directed to the polymorphic Forms A, B, C, D, E and F, and the amorphous form of Pitavastatin calcium salt (2:1).

One object of the invention is a crystalline polymorph of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt, herein designated as Form A, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 1 (vs = very strong intensity, s = strong intensity, m = medium intensity, w = weak intensity, vw = very weak intensity).

Table 1: d-spacings and 2θ angles for Form A.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
17.6	5.0	s
13.0	6.8	s
9.7	9.1	s
8.8	10.0	w
8.4	10.5	m
8.1	11.0	m
6.7	13.3	vw
6.5	13.7	s
6.3	14.0	w
6.0	14.7	w
5.57	15.9	vw
5.25	16.9	w
5.17	17.1	vw
4.82	18.4	m
4.64	19.1	w
4.27	20.8	vs
4.20	21.1	m
4.10	21.6	m
3.87	22.9	m
3.74	23.7	m
3.67	24.2	s
3.53	25.2	w
3.29	27.1	m
3.02	29.6	vw
2.95	30.2	w
2.63	34.0	w

Another object of the invention is a crystalline polymorph of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt, herein

designated as Form B, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 2.

Table 2: d-spacings and 2θ angles for Form B.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
19.0	4.6	w
16.6	5.3	vs
14.2	6.2	s
11.5	7.7	s
9.6	9.2	m
9.2	9.6	m
8.5	10.3	w
7.8	11.3	m
7.6	11.7	w
7.0	12.6	vw
6.8	13.0	w
6.4	13.9	m
6.0	14.7	vw
5.94	14.9	w
5.66	15.6	w
5.43	16.3	m
5.22	17.0	vw
5.10	17.4	vw
4.92	18.0	w
4.74	18.7	m
4.59	19.3	m
4.43	20.0	s
4.33	20.5	w
4.26	20.8	m
4.19	21.2	w, shoulder
4.13	21.5	m
3.97	22.4	m

3.83	23.2	s
3.73	23.8	m
3.64	24.4	vw
3.53	25.2	w, broad
3.42	26.0	w
3.37	26.4	vw
3.30	27.0	w
3.19	27.9	vw
3.09	28.9	w

Another object of the invention is a crystalline polymorph of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt, herein designated as Form C, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 3.

Table 3: d-spacings and 2θ angles for Form C.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
21.6	4.1	m
15.9	5.6	s
11.4	7.8	m
10.6	8.3	m
8.6	10.3	m
7.7	11.6	w
5.06	17.5	w
4.95	17.9	w
4.74	18.7	m
4.55	19.5	s
4.31	20.6	m
4.13	21.5	vw
4.06	21.9	m
3.84	23.1	m

3.71	24.0	w
3.58	24.8	w

Another object of the invention is a crystalline polymorph of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt, herein designated as Form D, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 4.

Table 4: d-spacings and 2θ angles for Form D.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
17.5	5.0	m
13.5	6.5	m
13.0	6.8	s
10.1	8.7	m
8.8	10.0	m
8.6	10.2	m
8.2	10.8	m
6.8	13.1	w
6.55	13.5	m
6.20	14.3	s
5.78	15.3	vw
5.52	16.1	m
5.28	16.8	w
4.87	18.2	w
4.80	18.5	m
4.66	19.0	w
4.46	19.9	m
4.34	20.5	m
4.23	21.0	vs
4.09	21.7	s
3.99	22.3	w

3.80	23.4	m
3.70	24.0	m
3.47	25.6	w
3.40	26.2	m

Another object of the invention is a crystalline polymorph of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt, herein designated as Form E, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 5.

Table 5: d-spacings and 2θ angles for Form E.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
20.0	4.4	vw
17.7	5.0	s
13.4	6.6	s
13.1	6.8	s
10.0	8.9	s
8.8	10.0	m
8.6	10.3	s
8.2	10.8	m
6.6	13.3	s
6.5	13.6	m
6.3	14.0	s
5.84	15.2	vw
5.56	15.9	w
5.39	16.4	w
5.24	16.9	vw
4.99	17.8	vw
4.84	18.3	m
4.69	18.9	w
4.39	20.2	vs

4.34	20.4	m
4.30	20.7	m
4.24	20.9	m
4.21	21.1	vs
4.12	21.6	m
4.08	21.7	m
3.99	22.3	m
3.77	23.5	m
3.73	23.8	m
3.69	24.1	w
3.60	24.7	vw
3.50	25.4	vw
3.35	26.6	m
2.96	30.2	w
2.64	34.0	vw

Another object of the invention is a crystalline polymorph of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt, herein designated as Form F, which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in d-values (Å) and in 2θ as given in Table 6.

Table 6: d-spacings and 2θ angles for Form F.

d-spacing [Å]	Angle [2θ]	Rel. Intensity
17.2	5.1	m
15.8	5.6	w
12.6	7.0	s
10.0	8.8	m
9.2	9.6	s
8.7	10.2	w
8.1	10.9	m
7.8	11.3	w

7.4	11.9	m
7.1	12.5	m
6.8	13.0	s
6.5	13.7	m
6.2	14.4	s
6.04	14.7	m
5.79	15.3	vw
5.70	15.5	w
5.28	16.8	m
5.03	17.6	w
4.85	18.3	m
4.61	19.3	m
4.51	19.7	m
4.30	20.6	m
4.18	21.2	vs
4.08	21.8	s
3.90	22.8	s
3.84	23.1	w
3.74	23.8	w, shoulder
3.69	24.1	s
3.59	24.8	s
3.46	25.7	m
3.40	26.2	vw
3.35	26.6	m
3.31	26.9	w
3.14	28.4	w
3.02	29.5	w
3.00	29.8	vw
2.89	30.9	m

Small changes in the experimental details can cause small deviation in the d-values and 2θ of characteristic peaks in the X-ray powder diffraction patterns.

Another object of the invention is the amorphous form of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt which exhibits characteristic X-ray powder diffraction patterns as depicted in Figure 7.

Powder X-ray diffraction is performed on a Philips 1710 powder X-ray diffractometer using Cu k(α1) radiation (1.54060 Å); 2θ angles are recorded with an experimental error of $\pm$ 0.1 – 0.2°. A discussion of the theory of X-ray powder diffraction patterns can be found in "X-ray diffraction procedures" by H.P. Klug and L.E. Alexander, J. Wiley, New York (1974).

Furthermore, the present invention is directed to processes for the preparation of Form A, B, C, D, E and F, and the amorphous form of Pitavastatin calcium.

Form A can be generally prepared from Pitavastatin sodium upon reaction with $CaCl_2$ in an aqueous reaction medium. Alternatively, Form A of the invention may also be obtained in situ from the free acid ((3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid) or the corresponding lactone with $Ca(OH)_2$, advantageously also in an aqueous reaction medium. The aqueous reaction medium usually contains at least 80 % b.w. of water; preferably it is water or water containing minor amounts of solvents and/or reactants from previous steps. Form A may contain up to 15% water, preferably about 3 to 12%, more preferably 9 to 11% of water.

Form B can be generally prepared by suspending form A in ethanol containing water as a co solvent. The amount of water is preferably about 1 to 50%.

Form C can be generally prepared by suspending form A in isopropanol containing water as a co solvent. The amount of water is preferably about 1 to 50%, especially 1 to 20% and more preferably about 5%. Form C can also be prepared from a mixture of isopropanol and a ketone solvent, containing water as a co solvent. Preferably, the ketone solvent is acetone, and the amount of ketone solvent are about 1 to 30%, more preferably about 10%. The amount of water is preferably about 1 to 20%, more preferably about 5%.

Form D can be generally prepared by suspending form A in absolute ethanol.

Form E can be generally prepared by suspending form A in 1,4-dioxane containing water as a co solvent. The amount of water is preferably about 1 to 50%.

Form F can be generally prepared by suspending form A in methanol containing water as a co solvent. The amount of water is preferably about 1 to 50%.

In the above mentioned processes small amounts of seeding crystals of the desired crystalline form may be added to the reaction mixture. Preferably small amounts are about 1 to 20 weight%, more preferably about 5 weight%. Seeding crystals may be added before or, where appropriate, after the step initiating the crystallization (e.g. cooling, addition of non-solvent etc. as described above). Addition before initiating the crystallization is of specific technical interest.

The amorphous form can be generally prepared by addition of a non-solvent to a concentrated solution of Pitavastatin calcium in an organic solvent. As non-solvent may be taken for example heptane or methyl tert-butyl ether, whereas examples for the organic solvent are 1,4-dioxane, tetrahydrofuran and ethyl methyl ketone. It is preferable that the non-solvent and solvent are miscible. The amorphous form can also be prepared by lyophilization of an aqueous solution of Pitavastatin calcium.

Preparations of polymorphic forms A, B, C, D, E, F as well as the amorphous form are usually done in substantially pure reaction systems, essentially consisting of the educt specified, preferably in substantially crystalline form, and solvents and/or non-solvents as given above.

Another object of the present invention are processes for the preparation of crystalline forms of Pitavastatin calcium essentially free of residual organic solvent.

Particularly, the present invention is related to processes for the preparation of crystalline forms of Pitavastatin calcium essentially free of residual organic solvent by exposing the crystalline form of Pitavastatin calcium to an atmosphere with a defined relative air humidity.

More particularly, the present invention is directed to a process for the preparation of any crystalline form or amorphous form of Pitavastatin calcium which is essentially free of residual organic solvent. These can, for example, be prepared by exposing the crystalline form or amorphous form to an atmosphere with a relative air humidity of 5 to 100%. Preferably, these are prepared by exposure to an inert gas stream with a defined relative air humidity to exchange residual organic solvent with water. In general, a relative air humidity of 5 to 100%, especially 40 to 80%, is used.

Another object of the present invention are pharmaceutical compositions comprising an effective amount of crystalline polymorphic Form A, B, C, D, E or F or the amorphous form of Pitavastatin calcium, and a pharmaceutically acceptable carrier.

These polymorphic forms may be used as single component or as mixtures with other crystalline forms or the amorphous form.

As to the novel polymorphic forms and amorphous form of Pitavastatin calcium it is preferred that these contain 25-100% by weight, especially 50-100% by weight, of at least one of the novel forms, based on the total amount of Pitavastatin calcium. Preferably, such an amount of the novel polymorphic forms or amorphous form of Pitavastatin calcium is 75-100% by weight, especially 90-100% by weight. Highly preferred is an amount of 95-100% by weight.

The compositions of the invention include powders, granulates, aggregates and other solid compositions comprising at least one of the novel forms. In addition, the compositions that are contemplated by the present invention may further include diluents, such as cellulose-derived materials like powdered cellulose, microcrystalline cellulose, microfine cellulose, methyl cellulose, ethyl cellulose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, carboxymethyl, cellulose salts and other substituted and unsubstituted celluloses; starch; pregelatinized starch; inorganic diluents like calcium carbonate and calcium diphosphate and other diluents known to the pharmaceutical industry. Yet other suitable diluents include waxes, sugars and sugar alcohols like mannitol and sorbitol, acrylate polymers and copolymers, as well as pectin, dextrin and gelatin.

Further excipients that are within the contemplation of the present invention include binders, such as acacia gum, pregelatinized starch, sodium alginate, glucose and other binders used in wet and dry granulation and direct compression tableting processes. Excipients that also may be present in the solid compositions further include disintegrants like sodium starch glycolate, crospovidone, low-substituted hydroxypropyl cellulose and others. In addition, excipients may include tableting lubricants like magnesium and calcium stearate and sodium stearyl fumarate; flavorings; sweeteners; preservatives; pharmaceutically acceptable dyes and glidants such as silicon dioxide.

The dosages include dosages suitable for oral, buccal, rectal, parenteral (including subcutaneous, intramuscular, and intravenous), inhalant and ophthalmic administration. Although the most suitable route in any given case will depend on the nature and severity of the condition being treated, the most preferred route of the present invention is oral. The dosages may be conveniently presented in unit dosage form and prepared by any of the methods well-known in the art of pharmacy.

Dosage forms include solid dosage forms, like tablets, powders, capsules, suppositories, sachets, troches and losenges as well as liquid suspensions and elixirs. While the description is not intended to be limiting, the invention is also not intended to pertain to true solutions of Pitavastatin calcium whereupon the properties that distinguish the solid forms of Pitavastatin calcium are lost. However, the use of the novel forms to prepare such solutions is considered to be within the contemplation of the invention.

Capsule dosages, of course, will contain the solid composition within a capsule which may be made of gelatin or other conventional encapsulating material. Tablets and powders may be coated. Tablets and powders may be coated with an enteric coating. The enteric coated powder forms may have coatings comprising phthalic acid cellulose acetate, hydroxypropylmethyl-cellulose phthalate, polyvinyl alcohol phthalate, carboxymethylethylcellulose, a copolymer of styrene and maleic acid, a copolymer of methacrylic acid and methyl methacrylate, and like materials, and if desired, they may be employed with suitable plasticizers and/or extending agents. A coated tablet may have a coating on the surface of the tablet or may be a tablet comprising a powder or granules with an enteric-coating.

Preferred unit dosages of the pharmaceutical compositions of this invention typically contain from 0.5 to 100 mg of the novel Pitavastatin calcium forms or mixtures thereof with each other or other forms of Pitavastatin calcium. More usually, the combined weight of the Pitavastatin calcium forms of a unit dosage are from 2.5 mg to 80 mg, for example 5, 10, 20 or 40 mg.

The following Examples illustrate the invention in more detail. Temperatures are given in degrees Celsius.

Example 1: Preparation of Form A

4.15 gr of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid tert-butyl ester (Pitavastatin tert-butyl ester) was suspended in 52 ml of a mixture of methyl tert-butyl ether and methanol (10:3). To this mixture were added 2.17 ml of a 4M aqueous solution of NaOH, and the resulting yellowish solution was stirred for 2.5 hours at 50°C. The reaction mixture was cooled to room temperature followed by the addition of 50 ml water and stirring for an additional hour. The aqueous phase was separated and once extracted with 20 ml of methyl tert-butyl ether. To this aqueous solution were added a solution of 0.58 gr $CaCl_2$ in 80 ml of water over a period of 1 hour. The resulting suspension was stirred for about 16 hours at room temperature. The suspension was filtered and the obtained solid was dried at 40°C and 50 mbar for about 16 hours. The obtained product is crystal Form A which is characterized by an X-ray powder diffraction pattern as shown in Figure 1. Further characterization of the obtained Form A by thermogravimetry coupled with FT-IR spectroscopy revealed a water content of about 10%. Differential scanning calorimetry revealed a melting point of 95°C.

Example 2: Preparation of Form B

100 mg Pitavastatin calcium Form A was suspended in 2 ml water and stirred at room temperature for 30 min, followed by the addition of 2 ml of ethanol and additional stirring for 18 hours. The suspension was filtered and dried in air, yielding 36 mg of Form B. The obtained crystal Form B is characterized by an X-ray powder diffraction pattern as shown in Figure 2. Further characterization of the obtained Form B by thermogravimetry coupled with FT-IR spectroscopy revealed a water content of about 10%.

Example 3: Preparation of Form C

62 mg Pitavastatin calcium Form A was suspended in 2 ml isopropanol containing 5% water. This suspension was heated to 60°C, which led to almost complete dissolution of Form A, and again cooled to room temperature. At this temperature the suspension was stirred for 66 hours. The resulting suspension was filtered, once washed with some isopropanol containing 5% water, and dried in air. The obtained crystal Form C is characterized by an X-ray powder diffraction pattern as shown in Figure 3. Further characterization of the obtained Form C by thermogravimetry coupled with FT-IR spectroscopy revealed that the sample contains about 6.3% isopropanol and a small amount of water.

Example 4: Preparation of Form C

65 mg Pitavastatin calcium Form A was suspended in a mixture of 0.9 ml isopropanol, 0.1 ml acetone and 40 µl water. Stirring this suspension for about 1 hour led to nearly complete dissolution. Seeding with 4 mg of Form C (from example 3) and stirring for 2 hours led to the formation of a concentrated suspension. This suspension was diluted with the same amount of solvent mixture as above and stirred for an additional 40 hours. The suspension was filtered and the obtained solid was dried at 40°C for about 10 min. Analysis by X-ray powder diffraction indicates the product to be crystal Form C as shown in Figure 3.

Example 5: Preparation of Form D

60 mg of Pitavastatin calcium Form A was suspended in 1 ml absolute ethanol and stirred at room temperature for 20 hours. The resulting suspension was filtered and dried in air. The obtained crystal Form D is characterized by an X-ray powder diffraction pattern as shown in Figure 4.

Example 6: Preparation of Form E

60 mg of Pitavastatin calcium Form A was suspended in a mixture of 1,4-dioxane and water (1:1), and stirred for 18 hours at room temperature. The resulting suspension was filtered and dried in air. The obtained crystal Form E is characterized by an X-ray powder diffraction pattern as shown in Figure 5.

Example 7: Preparation of Form F

60 mg of Pitavastatin calcium Form A was suspended in 3 ml methanol containing 20% water, and stirred at 40°C for 1 hour. The resulting suspension was slowly cooled to room

temperature and stirring was continued for 4 hours. The suspension was heated again to 40°C, stirred for 30 min, slowly cooled to room temperature and stirred for an additionally 15 hours. The suspension was filtered and the obtained white solid dried in air. The obtained crystal Form F is characterized by an X-ray powder diffraction pattern as shown in Figure 6.

Example 8: Preparation of the amorphous form

62 mg of Pitavastatin calcium Form A was dissolved in 0.3 ml 1,4-dioxane. To this stirred solution was slowly added 2.3 ml n-heptane at room temperature, and stirred for an additional 16 hours. The resulting suspension was filtered and dried in air. The obtained solid was amorphous as is shown by the X-ray diffraction pattern given in Figure 7 (top).

Example 9: Preparation of the amorphous form

60 mg of Pitavastatin calcium Form A was dissolved in 1.5 ml ethyl methyl ketone. To this solution was added in steps of 1 ml each 30 sec a total of 21 ml methyl tert-butyl ether. The resulting suspension was stirred at room temperature for about 16 hours. The suspension was filtered and the obtained solid was dried in air. An X-ray diffraction study on the product showed it to be amorphous, see Figure 7 (bottom). Further characterization of the obtained product by thermogravimetry coupled with FT-IR spectroscopy revealed that the sample contained about 5.5% methyl tert-butyl ether. Differential scanning calorimetry showed the sample to have a glass transition temperature of about 68°C.

Brief description of the drawings

Figure 1 is a characteristic X-ray powder diffraction pattern for Form A.
Figure 2 is a characteristic X-ray powder diffraction pattern for Form B.
Figure 3 are two characteristic X-ray powder diffraction patterns for Form C.
Figure 4 is a characteristic X-ray powder diffraction pattern for Form D.
Figure 5 is a characteristic X-ray powder diffraction pattern for Form E.
Figure 6 is a characteristic X-ray powder diffraction pattern for Form F.
Figure 7 are two characteristic X-ray powder diffraction patterns for the amorphous form.

Claims

1. A crystalline polymorph A of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 5.0 (s), 6.8 (s), 9.1 (s), 10.0 (w), 10.5 (m), 11.0 (m), 13.3 (vw), 13.7 (s), 14.0 (w), 14.7 (w), 15.9 (vw), 16.9 (w), 17.1 (vw), 18.4 (m), 19.1 (w), 20.8 (vs), 21.1 (m), 21.6 (m), 22.9 (m), 23.7 (m), 24.2 (s), 25.2 (w), 27.1 (m), 29.6 (vw), 30.2 (w), 34.0 (w); wherein (vs) stands for very strong intensity; (s) stands for strong intensity; (m) stands for medium intensity; (w) stands for weak intensity; (vw) stands for very weak intensity.

2. A crystalline polymorph A of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt having an X-ray powder diffraction pattern substantially as depicted in Figure 1.

3. A crystalline polymorph B of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 4.6 (w), 5.3 (vs), 6.2 (s), 7.7 (s), 9.2 (m), 9.6 (m), 10.3 (w), 11.3 (m), 11.7 (w), 12.6 (vw), 13.0 (w), 13.9 (m), 14.7 (vw), 14.9 (w), 15.6 (w), 16.3 (m), 17.0 (vw), 17.4 (vw), 18.0 (w), 18.7 (m), 19.3 (m), 20.0 (s), 20.5 (w), 20.8 (m), 21.2 (w, shoulder), 21.5 (m), 22.4 (m), 23.2 (s), 23.8 (m), 24.4 (vw), 25.2 (w, broad), 26.0 (w), 26.4 (vw), 27.0 (w), 27.9 (vw), 28.9 (w); wherein (vs) stands for very strong intensity; (s) stands for strong intensity; (m) stands for medium intensity; (w) stands for weak intensity; (vw) stands for very weak intensity.

4. A crystalline polymorph B of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt having an X-ray powder diffraction pattern substantially as depicted in Figure 2.

5. A crystalline polymorph C of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 4.1 (m), 5.6 (s), 7.8 (m), 8.3 (m), 10.3 (m), 11.6 (w), 17.5 (w), 17.9 (w), 18.7 (m), 19.5 (s), 20.6 (m), 21.5

(vw), 21.9 (m), 23.1 (m), 24.0 (w), 24.8 (w); wherein (s) stands for strong intensity; (m) stands for medium intensity; (w) stands for weak intensity; (vw) stands for very weak intensity. .

6. A crystalline polymorph C of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt having an X-ray powder diffraction pattern substantially as depicted in Figure 3.

7. A crystalline polymorph D of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 5.0 (m), 6.5 (m), 6.8 (s), 8.7 (m), 10.0 (m), 10.2 (m), 10.8 (m), 13.1 (w), 13.5 (m), 14.3 (s), 15.3 (vw), 16.1 (m), 16.8 (w), 18.2 (w), 18.5 (m), 19.0 (w), 19.9 (m), 20.5 (m), 21.0 (vs), 21.7 (s), 22.3 (w), 23.4 (m), 24.0 (m), 25.6 (w), 26.2 (m); wherein (vs) stands for very strong intensity; (s) stands for strong intensity; (m) stands for medium intensity; (w) stands for weak intensity; (vw) stands for very weak intensity.

8. A crystalline polymorph D of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt having an X-ray powder diffraction pattern substantially as depicted in Figure 4.

9. A crystalline polymorph E of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 4.4 (vw), 5.0 (s), 6.6 (s), 6.8 (s), 8.9 (s), 10.0 (m), 10.3 (s), 10.8 (m), 13.3 (s), 13.6 (m), 14.0 (s), 15.2 (vw), 15.9 (w), 16.4 (w), 16.9 (vw), 17.8 (vw), 18.3 (m), 18.9 (w), 20.2 (vs), 20.4 (m), 20.7 (m), 20.9 (m), 21.1 (vs), 21.6 (m), 21.7 (m), 22.3 (m), 23.5 (m), 23.8 (m), 24.1 (w), 24.7 (vw), 25.4 (vw), 26.6 (m), 30.2 (w), 34.0 (vw); wherein (vs) stands for very strong intensity; (s) stands for strong intensity; (m) stands for medium intensity; (w) stands for weak intensity; (vw) stands for very weak intensity.

10. A crystalline polymorph E of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt having an X-ray powder diffraction pattern substantially as depicted in Figure 5.

11. A crystalline polymorph F of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt which exhibits a characteristic X-ray powder diffraction pattern with characteristic peaks expressed in 2θ at 5.1 (m), 5.6 (w), 7.0 (s), 8.8 (m), 9.6 (s), 10.2 (w), 10.9 (m), 11.3 (w), 11.9 (m), 12.5 (m), 13.0 (s), 13.7 (m), 14.4 (s), 14.7 (m), 15.3 (vw), 15.5 (w), 16.8 (m), 17.6 (w), 18.3 (m), 19.3 (m), 19.7 (m), 20.6 (m), 21.2 (vs), 21.8 (s), 22.8 (s), 23.1 (w), 23.8 (w, shoulder), 24.1 (s), 24.8 (s), 25.7 (m), 26.2 (vw), 26.6 (m), 26.9 (w), 28.4 (w), 29.5 (w), 29.8 (vw), 30.9 (m); wherein (vs) stands for very strong intensity; (s) stands for strong intensity; (m) stands for medium intensity; (w) stands for weak intensity; (vw) stands for very weak intensity.

12. A crystalline polymorph F of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt having an X-ray powder diffraction pattern substantially as depicted in Figure 6.

13. The amorphous form of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt.

14. The amorphous form of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt having an X-ray powder diffraction pattern substantially as depicted in Figure 7.

15. A process for the preparation of a crystalline polymorph according to claim 1 or 2, which comprises the reaction of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid sodium salt with $CaCl_2$ in an aqueous reaction medium, or the reaction of the free acid (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid or the corresponding lactone with $Ca(OH)_2$.

16. A process for the preparation of a crystalline polymorph according to claim 3 or 4, which comprises suspending a crystalline polymorph according to claim 1 or 2 in ethanol containing water as a cosolvent.

17. A process according to claim 16, wherein the amount of water is 1 to 50% by volume of the suspension of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt.

18. A process for the preparation of a crystalline polymorph according to claim 5 or 6, which comprises suspending a crystalline polymorph according to claim 1 or 2 in isopropanol containing water as a cosolvent.

19. A process according to claim 18, wherein the amount of water is 1 to 50% by volume of the suspension of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt.

20. A process for the preparation of a crystalline polymorph according to claim 5 or 6, which comprises suspending a crystalline polymorph according to claim 1 or 2 in a mixture of isopropanol and a ketone solvent, containing water as a cosolvent.

21. A process according to claim 20 in which the ketone solvent is acetone.

22. A process according to claim 20 and 21, wherein the amount of ketone solvent is 1 to 30% by volume of the suspension of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt.

23. A process according to claim 20 to 22, wherein the amount of water is 1 to 20% by volume of the suspension of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt.

24. A process for the preparation of a crystalline polymorph according to claim 7 or 8, which comprises suspending a crystalline polymorph according to claim 1 or 2 in absolute ethanol.

25. A process for the preparation of a crystalline polymorph according to claim 9 or 10, which comprises suspending a crystalline polymorph according to claim 1 or 2 in 1,4-dioxane containing water as a cosolvent.

26. A process according to claim 25, wherein the amount of water is 1 to 50% by volume of the suspension of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt.

27. A process for the preparation of a crystalline polymorph according to claim 9 or 10, which comprises suspending a crystalline polymorph according to claim 1 or 2 in methanol containing water as a cosolvent.

28. A process according to claim 27, wherein the amount of water is 1 to 50% by volume of the suspension of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt.

29. A process according to any of the claims 15 to 28, wherein (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt is isolated by filtration and dried in air or vacuum.

30. A process according to any of the claims 15 to 29, wherein seeding is carried out with crystals of the desired crystalline polymorph.

31. A process for the preparation for the amorphous form according claim 13 or 14, wherein a non-solvent is added to a solution of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt in an organic solvent.

32. A process according to claim 31, wherein the non-solvent is selected from heptane and methyl tert-butyl ether.

33. A process according to claim 31 or 32, wherein the organic solvent is selcted from 1,4-dioxane, tetrahydrofuran and ethyl methyl ketone.

34. A process for the preparation for the amorphous form according claim 13 or 14, wherein an aqueous solution of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt is dried by lyophilization.

35. A process for the preparation of any crystalline form or the amorphous form of (3*R*,5S)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt essentially free of residual organic solvents by exposing this crystalline form or amorphous form to an atmosphere with a relative air humidity of 5 to 100%.

36. A process for the preparation of any crystalline form or amorphous form of (3*R*,5*S*)-7-[2-cyclopropyl-4-(4-fluorophenyl)quinolin-3-yl]-3,5-dihydroxy-6(*E*)-heptanoic acid hemicalcium salt essentially free or residual organic solvents by equilibrating this crystalline form or amorphous form in an inert gas flow with a relative air humidity of 5 to 100%.

37. A process according to claim 31 and 32 in which the relative air humidity is 40 to 80%.

38. A pharmaceutical composition comprising an effective amount of a crystalline polymorphic form according to one of claims 1 to 12 or the amorphous form according to claims 13 or 14, and a pharmaceutically acceptable carrier.

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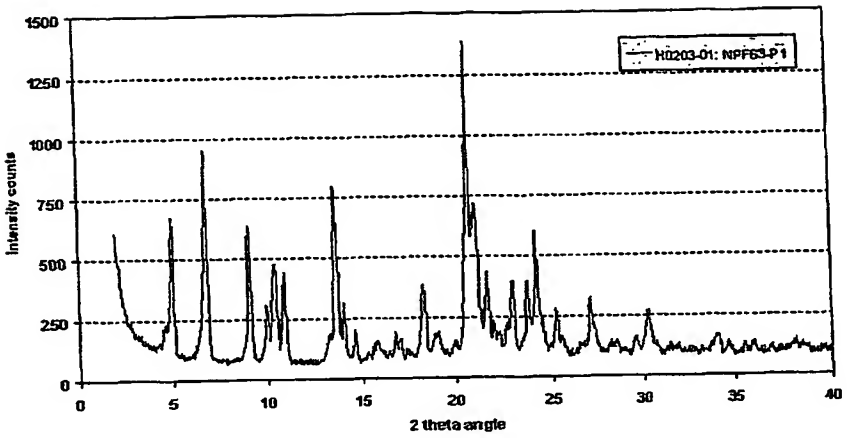
Figure 1: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2 / 7

Figure 2:

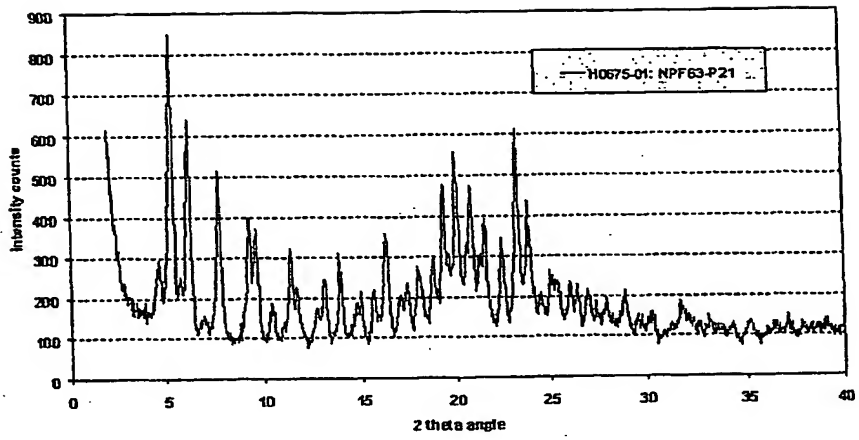
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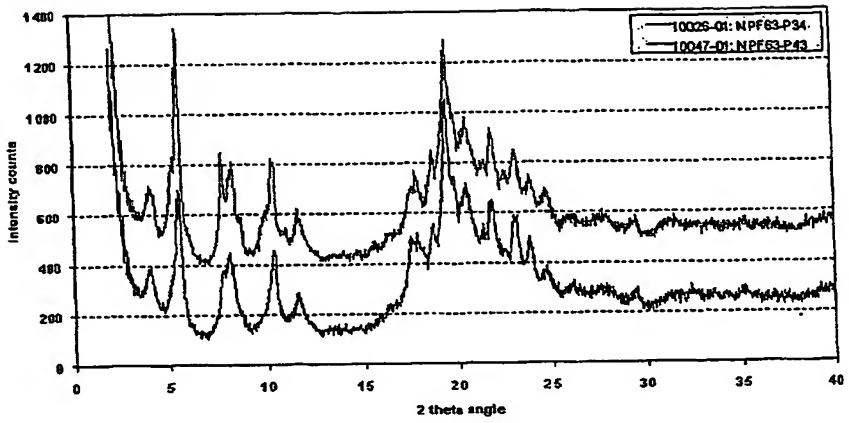
Figure 3: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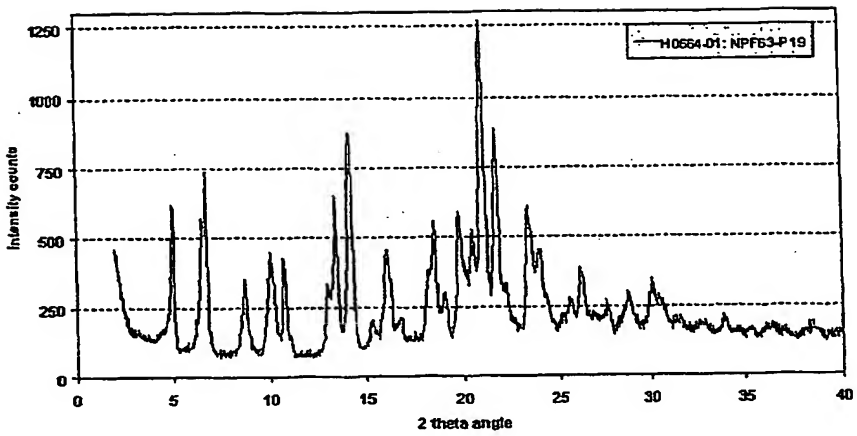
4 / 7

Figure 4: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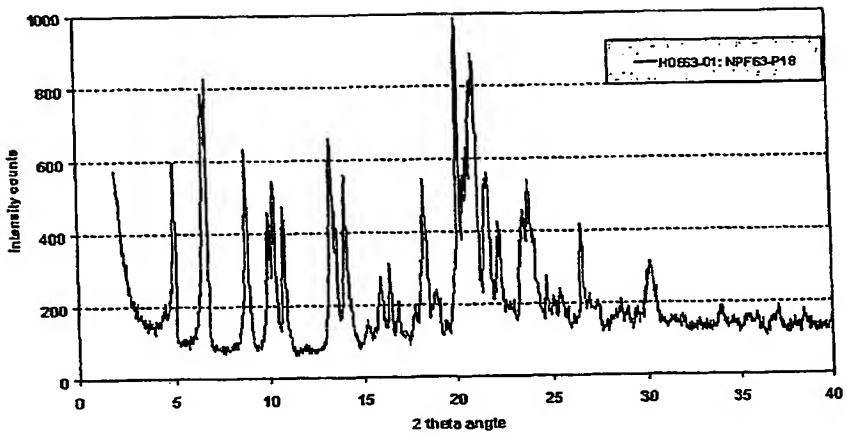
5 / 7

Figure 5: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6 / 7

Figure 6:

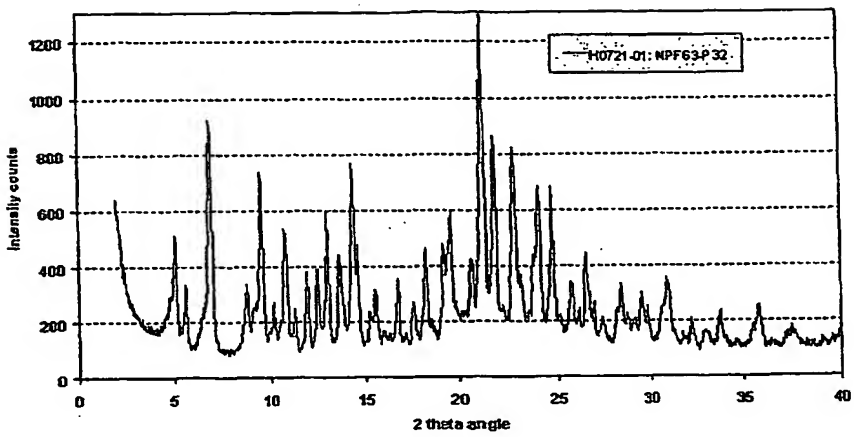
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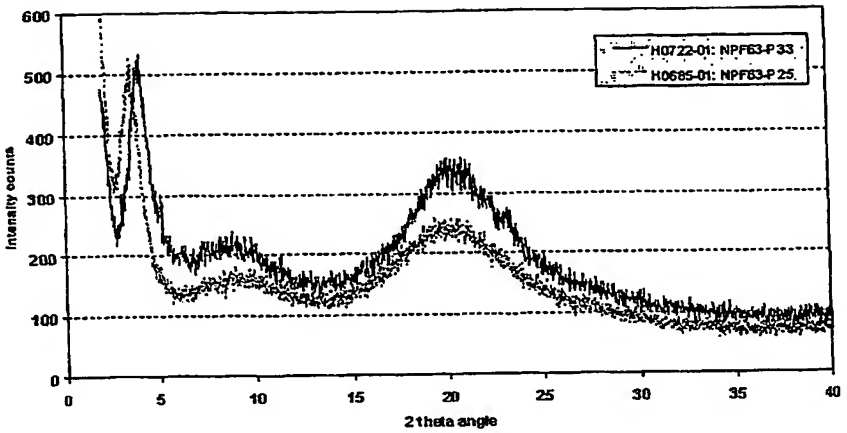
Figure 7: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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/050066

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/14 A61K31/47 A61P9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0 520 406 A (NISSAN CHEMICAL IND LTD) 30 December 1992 (1992-12-30) cited in the application example 3	1-15,38
X	SUZUKI M ET AL: "First Systematic Chiral Syntheses of Two Pairs of Enantiomers with 3,5-dihydroxyheptenoic Acid Chain, Associated with a Potent Synthetic Statin NK-104" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 20, 18 October 1999 (1999-10-18), pages 2977-2982, XP004180521 ISSN: 0960-894X cited in the application page 2979, line 11 - line 13	1,2,15, 38

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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"P" document published prior to the international filing date but later than the priority date claimed

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Date of the actual completion of the international search	Date of mailing of the international search report
21 June 2004	30/06/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bosma, P

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/050066

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 03/016317 A (NIDDAM-HILDESHEIM VALERIE ;TEVA PHARMA (IL); LIDOR-HADAS RAMI (IL)) 27 February 2003 (2003-02-27) page 15, line 6 - line 27; claims 5,8,11,19,22,24,28,38,41,42; examples 9,10	1-4, 15-17, 29,38

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP2004/050066

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP 0520406 A	30-12-1992	JP	5148237 A	15-06-1993
		AT	170513 T	15-09-1998
		CA	2072162 A1	25-12-1992
		DE	69226822 D1	08-10-1998
		DE	69226822 T2	11-02-1999
		DK	520406 T3	14-12-1998
		EP	0520406 A1	30-12-1992
		EP	0742209 A2	13-11-1996
		ES	2120973 T3	16-11-1998
		KR	208867 B1	15-07-1999
		US	5473075 A	05-12-1995
		US	5514804 A	07-05-1996
		US	5284953 A	08-02-1994
WO 03016317 A	27-02-2003	US	2002099224 A1	25-07-2002
		CA	2450820 A1	27-02-2003
		EP	1425287 A1	09-06-2004
		WO	03016317 A1	27-02-2003
		US	2003114685 A1	19-06-2003